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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LAVIN, CHRISTOPHER L	

ART UNIT	PAPER NUMBER
2624	

DATE MAILED: 07/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,638	NATTKEMPER ET AL.	
	Examiner	Art Unit	
	Christopher L. Lavin	2624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11 and 13-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on 04/18/06.

Claim Rejections - 35 USC § 103

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 1 – 3, 6 – 9, 11, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luck (5,257,182) in view of Watanabe (5,522,015).

In regards to claim 1 Luck discloses a method for analyzing microscope images comprising of the following steps:

a) Taking at least two microscope images of a sample including a plurality of biological objects (col. 4, lines 13 – 19);

b) Selecting a first microscope image and marking the positions (s) of mass gravity centers, i.e., centroids, of a number n of the individual objects discernible in the first microscope image, in which step each marked object is assigned a defined first image excerpt which completely surrounds the marked object, and each first image excerpt including a marked object, and each first image excerpt including a marked object is assigned the value 1, with the number n of such marked first image excerpts constituting a positive training set (col. 7, lines 46 – 53; col. 13, lines 17 – 23: Two training sets are disclosed, malignant and benign with a 0.9 and 0.1. Luck does not disclose using 1 and 0 for training a neural network. This will be shown to be well known in the art through Watanabe below. A complete training set consists of a positive (1) and

a negative (0) training set; col. 13, lines 40 – 48: the training set is based on "precisely the same type of net images" as were obtained for classification.);

c) Selecting and marking a number m of second image excerpts in said first microscope image each spaced a predetermined minimum distance from said first image excerpts, with a second image excerpt corresponding in size and shape to said first image excerpt, in which step each second image excerpt is assigned the value 0, with the number m of such marked second image excerpts constituting a negative training set (col. 7, lines 46 – 53; col. 13, lines 17 – 23; col. 8, lines 49 – 62; col. 13, lines 40 – 48: Two training sets are disclosed, malignant and benign with a 0.9 and 0.1. The training excerpts are chosen in exactly the same manner as the excerpts to be analyzed. Luck discloses that the image is processed to remove all objects larger than the objects of interest. So cell clumps will be removed; thus the only thing that will remain in the image after the processing is individual cells. Therefore cells that are touching would not remain. So only separate cells (at least 1 pixel of separation) will remain in the image, and therefore a minimum predetermined distance (1 pixel) is maintained between the first image excerpts and the second image excerpts.);

d) Determining characteristic features and/or feature combinations of the positive and negative training sets and assigning said characteristic features and/or feature combinations to a classification value between 0 and 1, said classification value representing the degree of probability of the presence of a marked object, and the determined features and/or feature combinations are stored (On page 7 of the applicant's remarks it is noted that step d is disclosed "at the top of p. 10 and continuing

for the rest of the page". Although step d is broad enough to cover the examiner's previous rejection, where the examiner believed that the content of page 9 described step d, in order to speed prosecution the examiner will provide a rejection that takes into account more clearly what the applicant views as what claim d is calling for. Therefore, based on the reading of page 10 in the specification it appears the applicant is simply describing the operations of a neural network. Where the classification value is in reference to the output of the neural network. Luck clearly discloses that the neural network is trained in exactly the same way as it used (col. 13, lines 40 – 48) and that the neural network outputs a classification value between 0.1 and 0.9, a 103 combination will be provided below teaching that a range of 0 to 1 could be substituted for the 0.1 to 0.9 range taught by Luck. It should be noted that although Luck does use more than one image to train the neural network, Luck does need to start with one image who's feature classifications will affect the classifications of all subsequent classifications by the neural network.);

e) Determine classification values of all image points of the second and each further microscope image by comparing the image data of the second and each further microscope image with the features and/or feature combinations in said first microscope image determined in procedural step d), in which step, for each image point of the second and each further microscope image, the classification value for an image excerpt surrounding the image point is determined and the size and shape of this image excerpt corresponds to the size and shape of the first or second image excerpt (col. 13, lines 17 – 23);

f) recognizing the position(s) of biological objects in the second or each further microscope image by evaluating the determined classification values, in which step the determined classification values are compared with a given threshold value representing the presence of a biological object, wherein classification values of all mage points of the second and each further microscope image are automatically determined according to the procedural step e) by scanning the image surface of the second and each further microscope image and wherein, further, the object positions determined by procedural steps a) to f) are compared in the total number of microscope images so as to obtain a spatial location and distribution of the individual objects in the sample (col. 14, lines 3 – 7; col. 14, lines 30 – 35).

Luck does not disclose using 1 and 0 for training a neural network. However, Watanabe (col. 5, lines 59 – 61) discloses using 1 and 0 to train a neural network. Luck discloses a method capable of classifying biological specimens on a microscope slide, however Luck has not specifically claim a threshold. However, Watanabe (col. 25, lines 42 – 44) discloses using a threshold of 0.5 to separate neural network outputs into two possibilities.

Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to use 0 and 1 to train a neural network as taught by Watanabe instead of 0.1 and 0.9 as taught by Luck. As the intent is to separate two types allowing more separation between the types will allow for better thresholding. Also to use thresholding for classification of neural network outputs (as disclosed by Watanabe) in the method disclosed by Luck allows for separation of the data into two subsets, as

Luck's method is designed to classify a cell as either malignant or benign thresholding will quickly and easily separate outputs for easy analysis.

With regards to claim 2, the method as claimed in claim 1 wherein the sample is a tissue sample and the biological object is a cell (Luck, col. 8, lines 33 – 35).

With regards to claim 3, the method as claimed in claim 1 wherein the biological objects to be determined are marked with one or plural chemical markers before the microscope images are taken (Luck, col. 8, lines 33 – 35).

With regards to claim 6, the method as claimed in claim 1 wherein the microscope images are taken by a CCD camera and then digitized (Luck, col. 7, lines 11 – 13).

With regards to claim 7, the method as claimed in claim 1 wherein the number n of the individual biological objects marked in procedural step b) is larger than or equal to 50 (Luck, col. 13, lines 17 –19: As "several hundred or thousands" of cells are used to create a training set inherently at least 50 of these biological objects would represent the positive (malignant) case.).

With regards to claim 8, the method as claimed in claim 1 wherein the first image excerpt is of square shape, with the size and/or side length of the first image excerpt corresponding at least to the maximum diameter of the biological objects in the first microscope image (Luck, col. 7, lines 49 – 59).

With regards to claim 9, the method as claimed in claim 1 wherein the number n of second image excerpts is larger than or equal to 50, with the second image excerpts being defined automatically, keeping to the minimum distance from the respective first

image excerpts (Luck, col. 13, lines 17 – 19: As "several hundred or thousands" of cells are used to create a training set inherently at least 50 of these biological objects would represent the negative (begin) case).

With regard to claim 11, the method as claimed in claim 1 wherein the threshold value of the classification value representing the presence of a biological object is at least 0.5 (Watanabe, Col. 25, lines 42 – 44).

With regards to claim 14, the method as claimed in claim 2 wherein the biological objects to be determined are marked with one or plural chemical markers before the microscope images are taken (Luck, col. 8, lines 33 – 35).

3. Claims 4, 5, 13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luck (as modified by Watanabe) as applied to claim 3 above, and further in view of Hemstreet (5,733,721).

Luck discloses a method for analyzing a microscope slide containing biological cells (col. 5, lines 16 – 21). Luck however does not teach how to prepare that slide or that fluorochrome should be used to mark the slide.

Hemstreet teaches that slides should be rinsed (col. 28, lines 27 – 32) before staining. Hemstreet then teaches that to create fluorescent images requires staining the slide with a fluorchrome (col. 7, line 64 – col. 8, line 6). Hemstreet then analyzes the fluorescent images with a neural network (col. 7, lines 47 – 51).

Luke (as modified by Watanabe) and Hemstreet are combinable because they are from the same field of endeavor, i.e., using neural networks to classify biological cells. It would have been obvious to one having ordinary skill in the art at the time of the

invention to prepare and stain the microscope slide (as taught by Hemstreet) before analyzing the microscope slide (as taught by Luke). A slide needs to be prepared in advance of use if the results are to be trusted. By staining the slide the method disclosed by Luke will have an easier time of identifying cells of interest.

With regards to claim 4, the method as claimed in claim 3 wherein the objects to be determined are marked with one or plural chemical markers before the microscope images are taken, with a bleaching or rinsing procedure being performed between the taking of the individual microscope images (Hemstreet, col. 28, lines 27 – 32).

With regards to claim 5, the method as claimed in claims 3 wherein said chemical markers are fluorochrome markers and the microscope images are fluorescence images (Hemstreet, col. 7, line 64 – col. 8, line 6).

With regards to claim 13, use of a method as claimed in claim 1 for the automatic cell classification of fluorescent cells (Luck, col. 3, lines 38 – 39; Hemstreet, col. 7, line 64 – col. 8, line 6).

With regards to claim 15, the method as claimed in claim 4 wherein said chemical markers are fluorochrome markers and the microscope images are fluorescence images (Hemstreet, col. 7, line 64 – col. 8, line 6).

Response to Arguments

4. Applicant's arguments filed 04/18/06 have been fully considered but they are not persuasive.

5. In response to the applicant's arguments over 112 rejections. With the applicant's assertion that step d is taught on page 10 and not page 9 the indefiniteness rejection is withdrawn.

6. In regards to applicant's argument "However, step b is carried out on the same microscope image, a "first" microscope image, not using "malignant and benign cells" as taught by Luck et al, which step clearly requires more than one microscope image." First the examiner must admit some confusion over this statement, the examiner does not see the correlation between the two items being compared. But in response, as previously shown Luck trains the neural network exactly the same as during the classification stage. And yes Luck most likely does use more than one image to create the overall training set, but the claims as currently written do not prohibit that. In fact it seems highly unlikely to the examiner that the applicant's own invention could function effectively if it only used one image. Most neural networks need hundreds and normally thousands of test data samples to become accurate, one image will not be able to provide enough information for training.

7. Next in regards to the confusion over the Watkins reference. The examiner would like to apologize for not removing all references to Watkins from the last action. Watkins was not being used in the rejections as stated in the last office action in response to the arguments. The few mentions of Watkins in the last action were simply the vestiges of the first office action.

8. In regards to applicant's arguments over Watanabe. Watanabe has been brought in to teach the concept that a neural network can be trained and output using

the values between 0 and 1. Luck teaches using 0.1 and 0.9, this is the only difference. Simple stretching out a range of a neural network is not novel, especially not when that range is well known as shown by Watanabe. As to the argument about "the same variable y" as mentioned in the last office action "In fact the examiner would like to point the applicant to the applicant's own specification page 9, lines 5 – 8 where the applicant also claims one variable, y, which can have two different values (1 or 0)."

9. In regards to applicant's response to the examiner about classifying cells based on positions. The examiner has carefully read over the portions of the specification pointed to by the applicant and still can find no mention of classifying cells based on position.

10. In regards to applicant's arguments with regards to the negative and positive training sets, the examiner maintains his previous reasoning provided in the last office action. The applicant is claiming two halves of a single training set. Also, the examiner would like to apologize for not contacting the applicant (as requested in the arguments over this issue); however do to time constraints the examiner was unable to fulfill this request. The applicant however is more than welcome to contact the examiner to discuss this or any other matters relating to the case.

Conclusion

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher L. Lavin whose telephone number is 571-272-7392. The examiner can normally be reached on M - F (8:30 - 5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bhavesh M. Mehta can be reached on (571) 272-7453. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christopher Lavin

BRIAN WERNER
PRIMARY EXAMINER